# ASSOCIATION BETWEEN STAVUDINE ADMINISTRATION WITH LIPODYSTROPHY AND DYSLIPIDEMIA AMONG HIV-INFECTED PATIENTS IN DR. KARIADI HOSPITAL SEMARANG

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# DECLARATION OF APPROVAL

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# HUBUNGAN ANTARA PEMBERIAN STAVUDINE DENGAN LIPODISTROFI DAN DISLIPIDEMIA PADA PENDERITA INFEKSI HIV DI RSUP DR. KARIADI SEMARANG

## ABSTRAK

Jacob Bunyamin[1], Muchlis A.U. Sofro[2]

**Latar belakang:** Pemberian stavudin (d4T) berkontribusi terhadap penurunan angka kematian pada penderita HIV. Di lain pihak, stavudin diketahui menimbulkan efek samping yang serius seperti lipodistrofi dan dislipidemia. Kedua efek samping tersebut dapat meningkatkan resiko terjadinya komplikasi pada jantung dan pembuluh darah.

**Tujuan:** Penelitian ini bertujuan untuk mengetahui hubungan antara pemberian stavudin dengan lipodistrofi dan dislipidemia pada penderita HIV di RSUP Dr. Kariadi dan juga mengetahui faktor-faktor yang berhubungan dengan lipodistrofi dan dislipidemia.

**Metode:** Penelitian ini adalah penelitian observasional analitik dengan metode belah lintang. Empat puluh sampel dibagi menjadi kelompok stavudin (23 sampel) dan kelompok kontrol (17). Seluruh responden diperiksa profil lipid dan lipodistrofi oleh dokter jaga di klinik VCT RSUP Dr. Kariadi. Data yang diperoleh dianalisis menggunakan uji Chi-Square dan uji Fisher.

**Hasil:** Prevalensi lipodistrofi sebesar 21,7% dan dislipidemia 82,6% pada kelompok stavudin. Pemberian stavudin berhubungan signifikan dengan dislipidemia (p=0.008) terutama pada kenaikan trigliserida dan penurunan kolesterol HDL (p=0.048 dan p=0.009). Pemberian stavudin tidak berhubungan signifikan dengan lipodistrofi (p=0.051) walaupun stavudin berhubungan dengan lipoatrofi pada pantat dan wajah (p=0.026 dan p=0.013). Jenis kelamin perempuan berhubungan dengan lipodistrofi pada kelompok stavudin (p=0.014). Jenis kelamin, umur, hitung CD4 dan durasi terapi tidak berhubungan dengan dislipidemia pada kelompok stavudin.

**Kesimpulan:** Pemberian stavudin berhubungan dengan dislipidemia pada penderita HIV di RSUP Dr. Kariadi dan tidak berhubungan dengan lipodistrofi.

**Kata kunci:** stavudin, lipodistrofi, dislipidemia, HIV

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# *ASSOCIATION BETWEEN STAVUDINE ADMINISTRATION WITH LIPODYSTROPHY AND DYSLIPIDEMIA AMONG HIV-INFECTED PATIENTS IN DR. KARIADI HOSPITAL SEMARANG*

## *ABSTRACT*

*Jacob Bunyamin[1], Muchlis A.U. Sofro[2]*

***Background:*** *Stavudine (d4T) administration has contributed in decreasing mortality rate of HIV-infected patients. In the other hand, stavudine is known to cause serious side effects such as lipodystrophy and dyslipidemia. Both side effects are known to increase the risk of developing cardiovascular complications.*

***Aims:*** *This study aimed to determine the association between stavudine administration with lipodystrophy and dyslipidemia among HIV-infected patients in Dr. Kariadi Hospital and also determine the factors associated with lipodystrophy and dyslipidemia.*

***Methods:*** *This study was an observational analytic study using cross-sectional method. Forty samples were divided into stavudine group (23 samples) and control group (17). All respondents had their lipid profile observed and lipodystrophy assessed by attending physicians in VCT clinic Dr. Kariadi Hospital. Obtained data were analyzed using Chi-Square Test and Fisher's Exact Test.*

***Results:*** *The prevalence of lipodystrophy was 21.7% and dyslipidemia was 82.6% in stavudine group. Stavudine administration was significantly associated with dyslipidemia (p=0.008) especially in triglycerides elevation and HDL-c depletion (p=0.048 and p=0.009). Stavudine administration was not significantly associated with lipodystrophy (p=0.051) although it was associated with lipoatrophy of buttock and face (p=0.026 and p=0.013). Being female was associated with lipodystrophy incidence in stavudine group (p =0.014). Sex, age, CD4 count, and duration of treatment were not associated with dyslipidemia in stavudine group.*

***Conclusion:*** *Stavudine administration was associated with dyslipidemia among HIV-infected patients in Dr. Kariadi Hospital and was not associated with lipodystrophy.*

***Keywords:*** *stavudine, lipodystrophy, dyslipidemia, HIV*

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## Background

The development of anti retroviral therapy (ART) has reduced mortality among HIV/AIDS patients. Coincident with these advances, was described a lipodystrophy syndrome occurring in patients taking ART. The syndrome is characterized by body fat redistribution and metabolic abnormalities. The metabolic disturbances reported are elevated triglyceride, cholesterol and fasting blood glucose level. A study taken in Uganda showed that prolonged exposure to ART in children contributes to metabolic changes thus increasing the cardiovascular risk of adulthood. It is proven that there is a direct connection between plasma cholesterol level and the arteriosclerotic process, especially the correlation between aortic fatty streaks in young persons with elevated serum cholesterol level.[1-3]

Stavudine, a Nucleoside Reverse Transcriptase Inhibitor (NRTI), has the highest propensity for causing mitochondrial dysfunction, yet it is relatively inexpensive and often has better availability in the developing world. According to 2013 WHO Antiretroviral Guidelines, stavudine administration should be discontinued due to its metabolic toxicities on mitochondria. A drug like stavudine has high capacity of inhibiting mtDNA γ-polymerase, which will cause mtDNA depletion and lipodystrophy as a further effect. A study in Western India showed that the prevalence of lipodystrophy was 46.1% and lipoatrophy was significantly associated with stavudine administration. A study in Tanzania resulted that 73% patients taking antiretroviral therapy suffered from dyslipidemia which was worse in patients who took stavudine.[4-8]

In Dr. Kariadi Hospital Semarang, there is little data known about the association between stavudine administration to lipodystrophy and dyslipidemia in Dr. Kariadi Hospital Semarang. The aim of this study is to determine the association between stavudine administration with lipodystrophy and dyslipidemia among HIV infected patients in Dr. Kariadi Hospital Semarang and also their associated routine demographic informations.

## Methods

This study was an observational analytic study using cross-sectional method. This study was conducted on March-May 2014. A preliminary survey was conducted on November 2013 – February 2014. The study took place in the Voluntary Counseling and Testing (VCT) Clinic of Dr. Kariadi Hospital Semarang. Samples were 40 HIV-infected patients administered with stavudine containing regimens in Dr. Kariadi Hospital for stavudine group (23 patients) and HIV-infected patients administered with zidovudine, lamivudine, and nevirapine for control group (17 patients).

The diagnosis of lipodystrophy was taken from Lipodystrophy Severity Grading Score (LSGS) sheet by attending physician in VCT clinic. Routine demographic informations such as age, sex, CD4 count, and duration of therapy were taken from case record forms. Patients were asked to fast overnight for 9 hours for lipid profile test. Lipid profiles checked were TG, TC, HDL-c, and

LDL-c blood level. A 5 ml blood sample was drawn from the patient's median cubital vein. The blood samples were analyzed using automated analyzer in Central Laboratory Dr. Kariadi Hospital Semarang.

Chi-square test was used to determine the association between age, sex, current CD4 count, and duration of therapy with the incidence of lipodystrophy and dyslipidemia. Ineligible data for chi-square test was analyzed using Fischer's Exact Test. All of data collections and research was under permission of the Commission of Health Research Bioethics Faculty of Medicine Diponegoro University/Dr. Kariadi Hospital Semarang Indonesia.

## Results and Discussions

**Table 1.** Samples Characteristics

| Characteristics | Stavudine Group n (%) | Control Group n (%) | P Value Lipodystrophy | P Value Dyslipidemia |
|---|---|---|---|---|
| Sex | | | **0.014** | 0.671 |
| Male | 12 (52.2) | 9 (52.9) | | |
| Female | 11 (47.8) | 8 (47.1) | | |
| Age (years) | | | 0.545 | 0.329 |
| Mean | 35.5 | 33.8 | | |
| Range | 24 – 58 | 22 – 50 | | |
| Duration of treatment (months) | | | 0.673 | 0.517 |
| Mean | 30.7 | 30.8 | | |
| Range | 9 – 121 | 6 – 72 | | |
| CD4 Count (cell/mm$^3$) | | | 0.128 | 0.614 |
| Mean | 234.6 | 264.2 | | |
| Range | 4 – 597 | 96 – 512 | | |
| ART regimens | | | | |
| d4T+3TC+ NVP | 6 (26.1) | - | | |
| d4T+3TC+EVF | 15 (65.2) | - | | |
| d4T+3TC+TDF | 2 (8.7) | - | | |
| ZDV+3TC+NVP | - | 17 (100) | | |

There were 21.7% patients with lipodystrophy in stavudine group. None of the patients in the control group acquired lipodystrophy. The prevalence is lower compared to a study in India, which was 46.1% for lipodystrophy.Another study in Australia reported that lipodystrophy in HIV-infected patients' prevalence reached 53%, in which 55% reported both peripheral lipoatrophy and central

lipohypertrophy, 31% with peripheral lipoatrophy only and 14% had central lipohypertrophy only. In Ethiopia, the prevalence was 68.3%.[7,9-10]

Dyslipidemia accounted in 82.6% of patients in stavudine group. This percentage is twice higher from the control group which was 41.2%. The percentage of normal lipid profile in stavudine group was 17.4% while the control group's was 58.8%. A study in Uganda showed that the prevalence of stavudine-associated dyslipidemia was 91%. A research in Kenya resulted that the prevalence of dyslipidemia was 63.1% in patients administered with stavudine.[11-12]

**Table 2.** Association between Stavudine and Lipodystrophy

| Variables | Stavudine Group | Control Group | *P* Value |
|---|---|---|---|
| | **n (%)** | **n (%)** | |
| Lipodystrophy | 5 (21.7) | 0 (0.0) | 0.051 |
| Absent | 18 (78.3) | 17 (100.0) | |
| Total | 23 (100.0) | 17 (100.0) | |

**Table 3.** Fat Distribution Changes Overview

| Variables | Stavudine group | | Control group | | *P* value |
|---|---|---|---|---|---|
| | **Fat distribution changes** | **Absent** | **Fat distribution changes** | **Absent** | |
| | **n (%)** | **n (%)** | **n (%)** | **n (%)** | |
| Lipoatrophy | | | | | |
| Upper arm | 4 (17.4) | 19 (82.6) | 0 (0.0) | 17 (100) | 0.097 |
| Thigh | 5 (21.7) | 18 (78.3) | 0 (0.0) | 17 (100) | 0.051 |
| Buttock | 6 (26.1) | 17 (73.9) | 0 (0.0) | 17 (100) | **0.026** |
| Face | 7 (30.4) | 16 (69.6) | 0 (0.0) | 17 (100) | **0.013** |
| Lipohypertrophy | | | | | |
| Abdomen | 8 (34.8) | 15 (65.2) | 6 (35.3) | 11 (64.7) | 0.616 |
| Breasts | 3 (13.0) | 20 (87.0) | 2 (11.8) | 15 (88.2) | 0.646 |
| Nuchae | 4 (17.4) | 19 (82.6) | 0 (0.0) | 17 (100) | 0.097 |
| Chin | 1 (4.3) | 22 (95.7) | 0 (0.0) | 17 (100) | 0.575 |

The statistical analysis showed that the administration of stavudine did not significantly correlate to lipodystrophy incidences in HIV-infected patients. A study in Rwanda found that stavudine administration had significant correlation with lipodystrophy (p=0.019). Van Griensven et al. showed that stavudine had significant association with facial lipodystrophy (p=0.011), thigh atrophy (p=0.006), and buttock atrophy (p=0.009) compared to zidovudine.[1,13]

These differences were likely caused by the lack of lipodystrophy definition in clinical settings. This study used Lipodystrophy Severity Grading Score (LSGS) measured by physical examination by attending physician while another study were conducted using data from patients' self reports or DEXA although Carter et al. stated that the results of both methods werely balanced. A study concluded that the prevalence of lipodystrophy would be different because of different definitions of lipodystrophy applied which may result in different statistical significance. The sample size of this study was also considered less compared to various studies in other countries. [14]

Sex was the only factor that significantly correlated with lipodystrophy in stavudine group ($p=0.014$). This finding was consistent with several studies conducted in Rwanda and South Africa which stated that being female was a significant risk factor in developing lipodystrophy. Females were also reported to have more central lipohypertrophy ($p<0.0001$), a pattern of lipodystrophy found most frequently in this study.Females were known to have impaired lipid profile due to the lack of 17-beta estradiol after menopause which increased LDL-c and decreased HDL-c levels, although the median age of this study was 35.5 years old.[10,13,15]

Meanwhile, age, duration of treatment and CD4 count did not have significant correlation with lipodystrophy in HIV-infected patients in Dr. Kariadi Hospital ($p=0.545$, $p=0.128$ and $p=0.673$).These findings were different with a study in Rwanda which stated that duration of treatment $\geq$ 18 months and CD4 count $\geq$150 cell/$mm^3$ had significant correlation with lipodystrophy ($p=0.020$ and $p=0.014$) while age was not significantly correlated ($p=0.328$). These differences may be caused by different sample size and different methods of diagnosing lipodystrophy.[13,16]

Although lipodystrophy is seen as cosmetic problem, the presence of lipodystrophy may suggest metabolical disturbance such as dyslipidemia, impaired glucose level, or hyperlactatemia. Clinically diagnosed lipodystrophy may become useful hints in detecting metabolic abnormalities in a resources limited setting. The presence of lipodystrophy may also cause stigma in HIV-infected patients and discrimination. Hadigan et al. found that among HIV-infected patients with lipoatrophy, the LDL-c particle exhibited a proatherogenic pattern.[17]

**Table 4.** Association between Stavudine and Dyslipidemia

| Variables | Stavudine Group | Control Group | *P* Value |
|---|---|---|---|
| | **n (%)** | **n (%)** | |
| Dyslipidemia | 19 (82.6) | 7 (41.2) | **0.008** |
| Normal | 4 (17.4) | 10 (58.8) | |
| Total | 23 (100.0) | 17 (100.0) | |

**Table 5.** Lipid Profile Changes Overview

| Variables | Stavudine group | | Control group | | *P* Value |
|---|---|---|---|---|---|
| | **Increased** | **Normal** | **Increased** | **Normal** | |
| | **n (%)** | **n (%)** | **n (%)** | **n (%)** | |
| TC (mg/dL) | 10 (43.5) | 13 (56.5) | 4 (23.5) | 13 (76.5) | 0.166 |
| TG (mg/dL) | 11 (47.8) | 12 (52.2) | 3 (17.6) | 14 (82.4) | **0.048** |
| HDL(mg/dL)[1] | 12 (52.2) | 11 (47.8) | 2 (11.8) | 15 (88.2) | **0.009** |
| LDL (mg/dL) | 8 (34.8) | 15 (65.2) | 2 (11.8) | 15 (88.2) | 0.096 |

[1] : Decreased HDL

Stavudine administration was significantly associated with dyslipidemia among HIV-infected patients in Dr. Kariadi Hospital. This result was consistent with a study taken in Uganda which also compared stavudine with zidovudine ($p=0.001$).[11]

Stavudine was significantly associated with elevated TG level and decreased HDL-c level. Administration of stavudine was not significantly correlated with both TC and LDL-c increases. This finding corresponded with the fact that dyslipidemia in HIV-infected patients is mostly characterized by hypertriglyceridemia and low HDL-c concentrations. Stavudine was also associated with higher TG elevation ($p<0.05$).[18-19]

This study found that sex, age, CD4 count, and duration of therapy had no significant association with dyslipidemia in stavudine group. This finding was similar with a study in Uganda which stated that sex, age, CD4 count, and duration of treatment had no significant association with dyslipidemia.[11]

Although being male and age $\geq$ 35 were considered as traditional risk factors of dyslipidemia, this finding was not seen in HIV-infected patients treated with stavudine in Dr. Kariadi Hospital. Confounding factors such as unhealthy diet, tobacco smoking and sedentary lifestyle may have role in impaired lipid profiles since most patients reported to do sport less than three times in a week and several patients claimed to have smoking history.

Peak body weight > 65 kg, family history of diabetes mellitus, family history of hypertension, and lipodystrophy were determined as risk factors for dyslipidemia in HIV-infected patients in Uganda. This study excluded patients with history of metabolic syndrome due to already impaired lipid profiles prior to stavudine administration.[11]

Elevated TG level is known as a risk factor of atherosclerosis which leads to heart attack and stroke. This impaired lipid profile may also cause pancreatic inflammation. The level HDL-c is a more potent risk factor for coronary heart disease compared to LDL-c level in blood. A study found that the risk of developing coronary heart disease decreases 2-3% for every 1 mg/dL increase of HDL-c. Pharmacological intervention and lifestyle modification should be promoted to patients with impaired lipid profiles. A reduction in dietary carbohydrate intake may improve an atherogenic lipid profile. [20]

It is recommended to switch stavudine with safer NRTI such as zidovudine (AZT) in limited resources area. Abacavir (ABC) and tenofovir (TDF) may be used if the situation is possible. Studies showed that either abacavir or tenofovir administration may improve increased lipid profiles caused by stavudine although abacavir did not reverse lipodystrophy effectively.[21-22]

Several limitations of this study were the sample size was not large compared to other studies conducted in different countries. We also could not determine the association between Body Mass Index (BMI) with lipodystrophy and dyslipidemia because the lack of data needed to assess BMI of HIV-infected patients in Dr. Kariadi Hospital Semarang.

## Conclusions

Stavudine administration was significantly associated with dyslipidemia among HIV-infected patients in Dr. Kariadi Hospital and was not associated with lipodystrophy. Sex was siginificantly associated with lipodystrophy in stavudine group while age, CD4 count, and duration of treatment were not. None of the routine demographic informations were significantly associated with dyslipidemia in stavudine group.

## Suggestions

Stavudine should be phased out as first-line drugs in HIV treatment in Dr. Kariadi Hospital Semarang due to its metabolic side effects such as dyslipidemia and lipodystrophy. Zidovudine, abacavir or tenofovir should be used to replace stavudine due to its ability to improve disturbed lipid profiles in patients with stavudine associated dyslipidemia.

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